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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/826,082 | 04/15/2004 | Timothy C. Wang | UMY-043 | 1338 |

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| EXAMINER | |
|---|---|
| BELYAVSKYI, MICHAIL A | |
| ART UNIT | PAPER NUMBER |
| 1644 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/826,082 | WANG ET AL. | |
| | Examiner | Art Unit | |
| | Michail A. Belyavskyi | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-4,13-22 and 28-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 13-22 and 28-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 05/27/05 is acknowledged.

Claims 1-4, 13-22 and 28-33 are pending.

*Claims 1-4,13-22 and 28-33 read on a method of determining whether a subject has an bone marrow derived stem cell dependent metaplasia, comprising detecting the presence of mesenchymal stem cell (MSC) or MSC derived cell in a test sample are under consideration in the instant application.*

In view of the amendment, filed 05/25/07 the following rejection remains:

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

3. Claims 1-4, 13-22 and 28-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons set forth in the previous Office Action, mailed on 12/26/06.

Applicant's arguments, filed 05/25/07 have been fully considered, but have not been found convincing .

Applicant asserts that as amended claims are directed to a methods determining whether a subject has a BMDC dependent metaplasia, comprising detecting the presence of a MSC or MSC derived cell in a test sample. Applicant discovered that it is this specific population of BMDC that are the primary source of metaplasia and cancer ( as shown in Example I). Applicant point the Examiner to overlapping pages 16-28 of the instant Specification, wherein a plethora of art known diagnostic and prognostic methods are disclosed.

Contrary to Applicant's assertion, the issue raised in the previous Office Action was not about art recognized diagnostic or prognostic methods. The Examiner acknowledge that at the time the invention was made one skill in the art would know how to determine the presence of the presence of a MSC or MSC derived cell in a test sample.

However, as has been stated in the previous Office Action, the specification only discloses that : (i) BMDC are involved in healing of acute gastric ulvers ( see Example 1 in particular) , (ii) inflammation and tissue loss secondary to chronic gastric *Helicobacter* infection represent a sufficient stimulus for long-term engraftment and homing of BMDC that might contribute over time to metaplasia, dysplasia and cancer( see Example 2 and 3 in particular). It is noted however, that specification disclosed that "**in our system we believed** that MSC is the most likely cell type responsible for engraftment seen ( emphases added, see page 61 in particular). The Specification farther disclosed that it is suggested that the quality as well as the quantity and duration of inflammation plays a central role in the degree of maladaptive differentiation of the BMDC once it resides in the peripheral tissue . **The concept that cancer can arise from BMDC** would alter greatly our understanding of cancer intitiation and progression ( emphases added). In other words, the Specification only prophetically suggested that MBDC might contribute to cancer.

With regards to Applicant statement that " Applicant discovered that MSC or MSC derived cell are the primary source of metaplasia and cancer as shown in Example I."

The Examiner disagrees with said statement. At page 57 the instant specification disclosed that " in our long term infected model , the majority of dysplastic gland and all of the intraepithelial neoplasia arose from donor marrow supporting our hypothesis that this population of cells is inherently vulnerable to malignant transformation". In other words Applicant acknowledge that it is only **a hypothesis** that said population can be vulnerable to malignant transformation ( emphases added). Clearly one skill in the art would not considered that said statement as a solid evidence of the existence of direct correlation between the presence of MSC or MSC derived cell and probability that the subject has BMDC-associated cancer or BMDC dependent metaplasia. Moreover, as acknowledge by Applicant, the fact that MSC or MSC derived cells are the primary source of metaplasia was surprising discovery ( see page 11 of Applicant's arguments filed on 05/25/07). As such, the invention must be considered unpredictable.

The Specification provide no evidences that the presence of presence of MSC or MSC derived cell in a test sample from the subject is an indicative that the subject has BMDC-associated cancer or BMDC dependent metaplasia or has a higher than normal risk of developing either an BMDC-dependent metaplasia or BMDC-associated cancer. Moreover, no animals models were used to study the effectively of a method of determining whether a subject has an BMDC dependent metaplasia or a method of determining whether a subject has BMDC-associated cancer or a subject has a higher than normal risk of development an BMDC dependent metaplasia or BMDC-associated cancer, each comprising detecting the presence of MSC or MSC derived cell in the test sample from the subject . Since there is no animal model studies and data in the specification to show the effectively of a method of determining whether a subject has an

BMDC dependent metaplasia or a method of determining whether a subject has BMDC-associated cancer or a subject has a higher than normal risk of development either an BMDC dependent metaplasia or BMDC-associated cancer, each comprising detecting the presence of MSC or MSC derived cell in the test sample from the subject it is unpredictable how to correlate disclosed data with the claimed intended use. Lyden et al., ( Nature Medicine, 2001, Vol.7, page 1194-1201) teach that it is not yet established whether BM-derived precursor cells can contribute to tumor neo-angiogenesis ( see entire document, Abstract in particular). Feldman et al (Transplant. Proc. 1998, 30, 4126-4127) teach that "while it is not difficult to study the pathogenesis of animal models of disease, there are multiple constraints on analyses of the pathogenesis of human disease, leading to interesting dilemmas such as how much can we rely on and extrapolate from animal models in disease". Mestas et al ( J. of Immunology, 2004, 172, pages 2731-238) teach that there exist significant differences between mice and humans in immune system development, activating and response to challenge in both the innate and adaptive arms. As therapies for human diseases become ever more sophisticated and specifically targeted it becomes increasing important to understand the potential limitations of extrapolating data from mice to humans. The literature is littered with the examples of therapies that work well in mice but fail to provide similar efficacy in humans.

Thus , one skill in the art can not predict the efficiency of: (i) a method of determining whether a subject has an BMDC dependent metaplasia, claimed in claim 1, or a method of determining whether a subject has BMDC-associated cancer, claimed in claim 2 or a subject has a higher than normal risk of development an BMDC dependent metaplasia, claimed in claim 3 or BMDC-associated cancer, claimed in claim 4, each comprising detecting the presence of MSC or MSC derived cell in the test sample from the subject . Thus in the absence of working examples or detailed guidance in the specification, the intended uses of a method of determining whether a subject has an BMDC dependent metaplasia or a method of determining whether a subject has BMDC-associated cancer or a subject has a higher than normal risk of development an BMDC dependent metaplasia or BMDC-associated cancer, each comprising detecting the presence of MSC or MSC derived cell in the test sample from the subject are fraught with uncertainties.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed (i) a method of determining whether a subject has an BMDC dependent metaplasia, claimed in claim 1, or a method of determining whether a subject has BMDC-associated cancer, claimed in claim 2 or a subject has a higher than normal risk of development an BMDC dependent metaplasia, claimed in claim 3 or BMDC-associated cancer, claimed in claim 4, each comprising detecting the presence of MSC or MSC derived cell in the test sample from the subject in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

4. No claim is allowed.

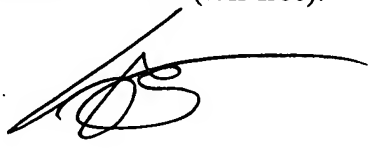
5. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/ 272-0840 The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/ 272-0841 .

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



MICHAIL BELYAVSKYI, PH.D.
PATENT EXAMINER

08/03/07